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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,169	06/08/2001	Clemens Antoni Van Blitterswijk	04148-00012	9604

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,169	VAN BLITTERSWIJK ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,16-18,20-22,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,16-18,20-22,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 September 2004 has been entered.

Status of Application, Amendments and/or Claims

The amendment filed 29 September 2004 has been entered in full. Claims 1-9, 11-15, 19, 23, 24, 27 and 28 are cancelled. Claims 10, 16-18, 20-22, 25 and 26 are under examination.

The information disclosure statement (IDS) filed 29 September 2004 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection to claims 20-22 under 35 U.S.C. 112, first paragraph, scope of enablement, as set forth at pages 2-5 of the previous Office Action (29 June 2004) is *withdrawn* in view of the amendment (29 September 2004).

The rejection to claims 25 and 26 under 35 U.S.C. 112, first paragraph, enablement, as set forth at page 6 of the previous Office Action (29 June 2004) is *withdrawn* in view of the amendment (29 September 2004).

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

Claims 10, 16-18 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of producing osteocalcin comprising the steps of

(a) applying bone marrow cells on a substrate

(b) contacting the bone marrow cells with a culture medium

(c) inducing the bone marrow cells to differentiate into osteogenic tissue by one or more inductors of differentiation, wherein osteogenic tissue produce osteocalcin

(d) recovering osteocalcin from the culture medium,

does not reasonably provide enablement for: a method of producing osteocalcin comprising the steps of

(a) applying undifferentiated mammalian cells on a substrate;

(b) contacting the undifferentiated mammalian cells with a culture medium;

(c) inducing the undifferentiated mammalian cells to differentiate into osteogenic tissue by one or more inductors of differentiation, wherein osteogenic tissue produce osteocalcin, and;

(d) recovering osteocalcin from the culture medium.

The basis for this rejection is set forth at pages 2-6 of the previous Office Action (29 June 2004).

Applicant reiterate that methods of applying undifferentiated cells on a substrate, contacting the cells with a culture medium, inducing the undifferentiated cells to differentiate and produce active factors and recovering active factors from the culture medium use techniques that are well known by those of skill in the art fields such as cell culture, cell biology, transplantation and the like. Applicant argues that a working example is provided wherein undifferentiated cells are added to a substrate in the presence of culture medium, the cells are induced to differentiate into cells having osteogenic character and osteocalcin is produced. Applicant contends that the Examiner indicated that the instant specification is enabling for a method of producing osteocalcin.

Applicant's arguments have been fully considered but not deemed persuasive for the following reasons. The scope of patent protection sought by Applicant as defined by the claims fails to bear a reasonable correlation with the scope of an enabling disclosure set forth in the specification because the instant specification fails to teach that any type of undifferentiated mammalian cell can differentiate into osteogenic cells and produce osteocalcin. Examples 1-4 from the instant specification teach that rat ***bone marrow***

(***not undifferentiated cells***) cultured in medium develop into opaque, three dimensional mineralized nodular structures after two weeks (page 5, lines 1-16). The specification states that the osteogenic character of rat bone marrow culture system has been well characterized using a number of criteria (page 5, lines 21-34). The specification teaches that osteocalcin bone protein is released in the medium (page 6, lines 4-5 and page 12, lines 15-16). The specification teaches that bone marrow cells supplemented with media differentiated into osteoclast, which produced osteocalcin bone protein.

The instant claims are broadly drawn to "any" undifferentiated mammalian cell. An undifferentiated mammalian cell has the potential to differentiate into any cell type (i.e. neuronal, heart, lung, etc). The specification is not enabling for this limitation. The instant claims encompass a genus (undifferentiated mammalian cells), while the specification teaches a species (bone marrow cells). The instant claims are so broad with respect to the disclosure that undue experimentation would be required of the skilled artisan to discern if any undifferentiated mammalian cell had the potential to differentiate into osteogenic cells in the presence of one or more inductors of differentiation and produce osteocalcin. There is a high level of unpredictability regarding the potential of any undifferentiated mammalian cells to differentiate into an osteogenic cell and produce osteocalcin. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Due to the large quantity of experimentation necessary to induce any type of undifferentiated mammalian cell to differentiate into osteogenic cells by one or more

inductors of differentiation and recover osteocalcin, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite limitations regarding the types of undifferentiated mammalian cells that can be employed in the claimed method, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10, 16-18, 20-22, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Gronthos *et al.* (Blood, Vol. 84, No. 12, 4164-4173, 1994, IDS submitted by Applicant 12/02).

The instant claims are drawn to a method of producing osteocalcin comprising the steps of (a) applying undifferentiated mammalian cells {or bone marrow cells (comprising stromal cells)} on a substrate; (b) contacting the undifferentiated mammalian cells {or bone marrow cells (comprising stromal cells)} with a culture medium; (c) inducing the undifferentiated mammalian cells {or bone marrow cells (comprising stromal cells)} to differentiate into osteogenic tissue by one or more

inductors of differentiation, wherein osteogenic tissue produce osteocalcin, and; (d) recovering osteocalcin from the culture medium.

Gronthos *et al.* teach the culturing of bone marrow stromal cell progenitors (fibroblast colony-forming units, CFU-F) from adult human bone marrow (abstract and page 4165, first paragraph and materials and methods). These cells were capable of forming a layer *in vitro* consisting of stromal cell types (page 4165, first paragraph). After two weeks of culture, all of the CFU-colonies grown in the presence of ASC-2P, DEX and PO4 were found to express alkaline phosphatase, which is a well-documented marker of bone cell differentiation (page 4167, 2nd paragraph). The adherent layers of bone marrow cultures after 4 weeks in osteogenic conditions displayed large areas of mineralized material (page 4167, 3rd paragraph). Six-week-old mineralized bone marrow cultures were washed in PBS and serum starved. The biosynthesis of osteocalcin was stimulated by the addition of 1,25-Vit D3. Samples were taken from the medium of the cultures and analyzed for the presence of osteocalcin (page 4168, last paragraph). Gronthos *et al.* teach that primary human bone cells have been shown to synthesize osteocalcin in the presence of 1,25-Vit D3.

Gronthos *et al.* state that in the present study comparable levels of osteocalcin were found in the culture medium of human BM cultures induced for 6 weeks under osteogenic conditions and stimulated with 1,25-Vit D3 for 48 hours. Gronthos *et al.* teach that their work provides direct evidence that purified human BM CFU-F under defined *in vitro* culture conditions are capable of osteogenic differentiation (page 4141, 3rd-4th paragraph).

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-22, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maniatopoulos *et al.*, Cell Tissue Research 254:317-330 (1988).

The instant claims are drawn to a method of producing osteocalcin comprising the steps of (a) applying undifferentiated mammalian cells {or bone marrow cells (comprising stromal cells)} on a substrate; (b) contacting the undifferentiated mammalian cells {or bone marrow cells (comprising stromal cells)} with a culture medium; (c) inducing the undifferentiated mammalian cells {or bone marrow cells (comprising stromal cells)} to differentiate into osteogenic tissue by one or more inductors of differentiation, wherein osteogenic tissue produce osteocalcin, and; (d) recovering osteocalcin from the culture medium.

Maniatopoulos *et al.*, teach the application of rat bone marrow stromal cells in culture medium (page 318, 1st-3rd paragraph and page 320, subculture paragraph). Maniatopoulos *et al.*, teach that the bone like matrix of the nodules was stained by antibodies to osteocalcin (page 323, immunohistochemistry paragraph). Maniatopoulos *et al.*, teach that mineralized bone like nodules were produced by bone marrow stromal cells cultured *in vitro* and believe it to be the first report of the expression of bone like

tissue *in vitro* by bone marrow stromal cells (page 325, discussion). Maniatopoulos *et al.* teach that osteocalcin is believed to be exclusively synthesized by cells associated with mineralized tissue (top of page 327). Maniatopoulos *et al.* teach that the key factor in the producing bone like nodules was the presence in the medium of dexamethasone, a synthetic glucocorticoid and that it has been suggested that glucocorticoids induce proliferation and terminal differentiation of osteogenic cells (page 327, 4th paragraph).

Maniatopoulos *et al.* do not actually recover osteocalcin from the culture media. However, upon reading the reference, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Maniatopoulos *et al.* Based on light microscopy and immunohistochemistry staining with osteocalcin antibodies, Maniatopoulos *et al.* demonstrate that rat bone marrow cells can differentiate into osteogenic tissue and produce osteocalcin. Thus, the motivation and expected success is provided by the *in vitro* system of Maniatopoulos *et al.*, which would allow one to employ bone marrow cells comprising stromal cells to differentiate into osteogenic tissue and produce and isolate osteocalcin.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

RMD
12/17/04